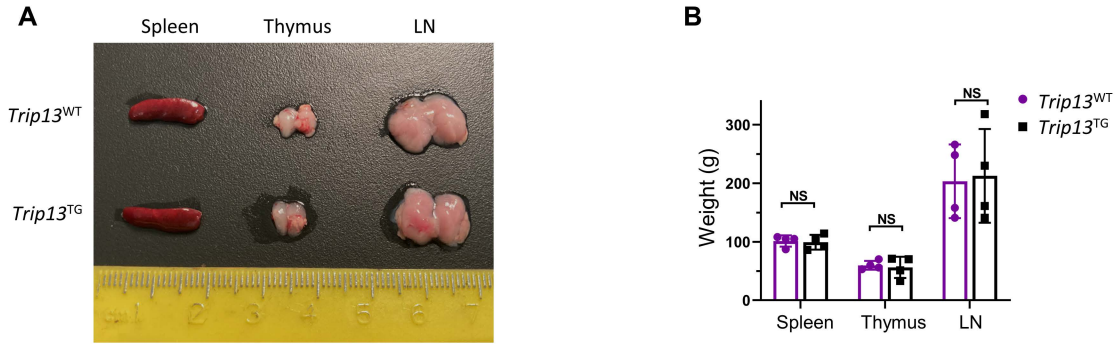
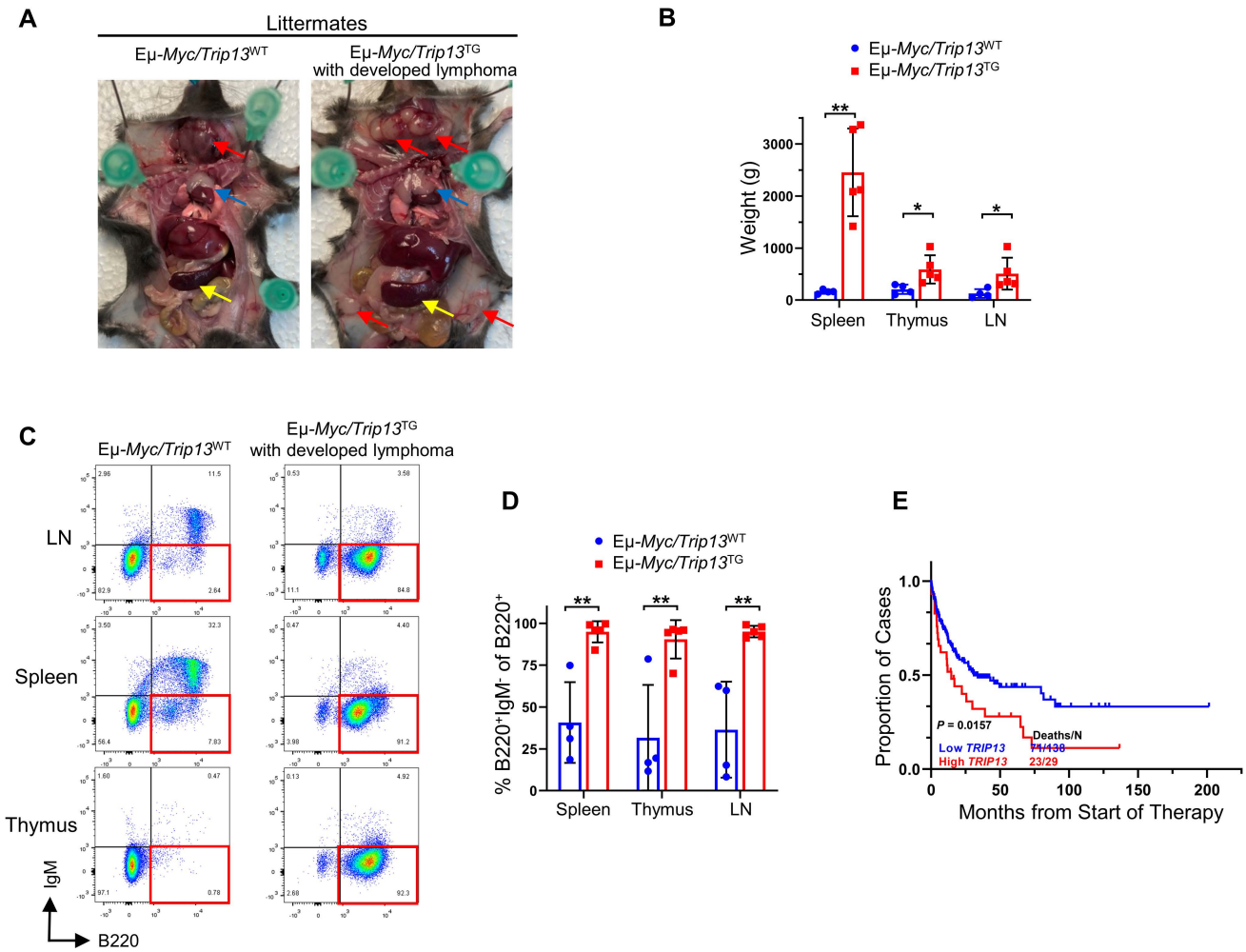
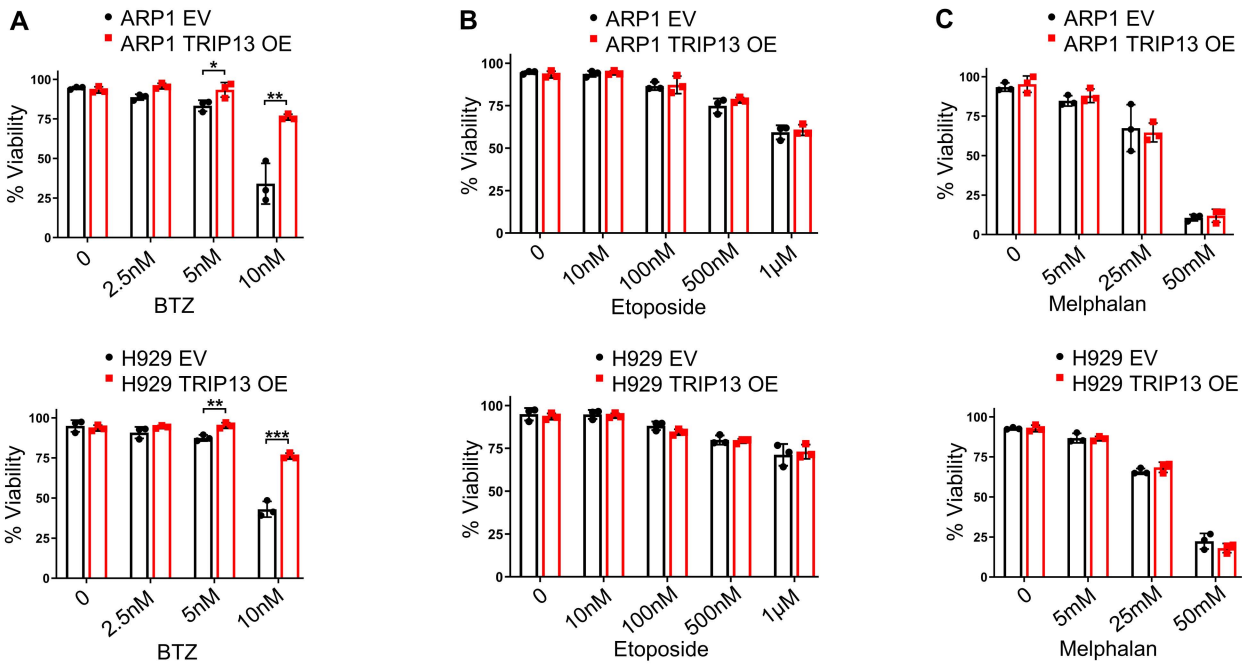


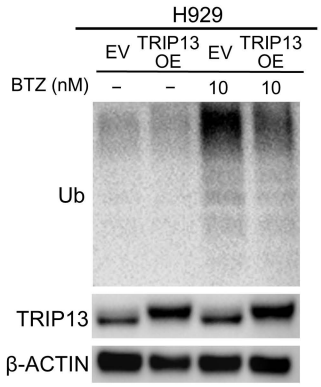
Supplemental Figure 1. Comparison of lymphoid tissue between *Trip13*^{TG} and *Trip13*^{WT} littermate control mice. (**A**) Representative images showing no tissue size difference of spleen, thymus and cervical lymph nodes (LN) between *Trip13*^{TG} and *Trip13*^{WT} littermate control mice. (**B**) Weight of spleen, thymus and cervical LN of *Trip13*^{TG} mice (*n*=4) compared to*Trip13*^{WT} littermate controls (*n*=4). Data are presented as mean ± SD. NS, no significance by Student's *t* test. The number of evaluated mice is indicated between parentheses.



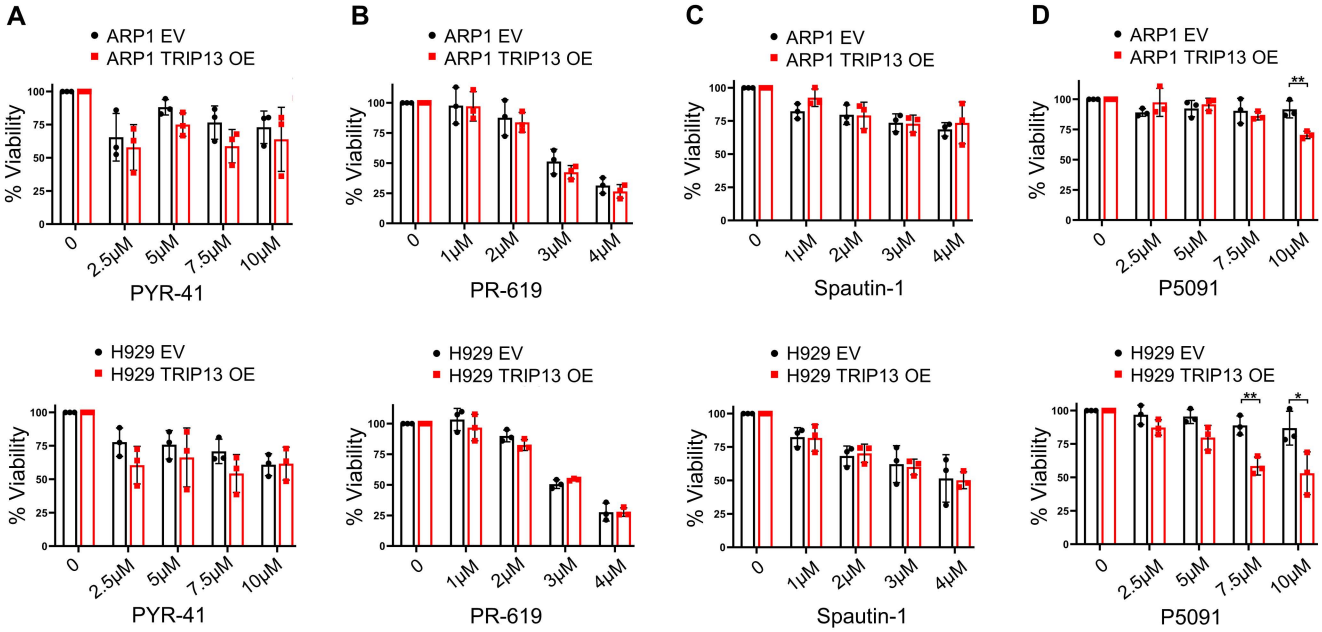
Supplemental Figure 2. TRIP13 accelerates tumorigenesis in Eμ-*Myc* mouse model and is linked to poor prognosis in patients with B-cell malignancies. (**A**) Representative images showing pronounced enlarged cervical and inguinal lymph nodes (LN, red arrow), spleen (yellow arrow) and thymus (blue arrow) of Eμ-*Myc/Trip13*^{TG} mice compared to Eμ-*Myc/Trip13*^{WT} littermate control. (**B**) Weight of cervical, axillary and inguinal LN, spleen and thymus of Eμ-*Myc/Trip13*^{TG} mice (n=5) compared to Eμ-*Myc/Trip13*^{WT} littermate controls (n=4). (**C**) Representative flow cytometry plots showing dominantly B220^{+}IgM^{-} B-cell lymphoma population (red box) in spleen, thymus and LN of Eμ-*Myc/Trip13*^{TG} mice compared to Eμ-*Myc/Trip13*^{WT} littermate control. (**D**) Flow cytometry quantification of B220^{+}IgM^{-} B-cell lymphoma population percentage in B220^{+} total B cells of corresponding tissues from (**B**). Data in (**B**) and (**D**) are presented as mean ± SD. * $P < 0.05$, ** $P < 0.01$ by Student's t test. The number of evaluated mice is indicated between parentheses. (**E**) Kaplan-Meier analysis of ABC DLBCLs with high versus low *TRIP13* (Best cut off, $P = 0.0157$ by log-rank test).



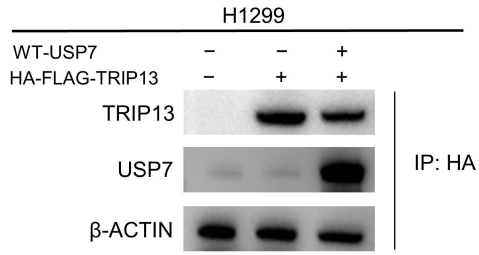
Supplemental Figure 3. High TRIP13 shows drug resistance to BTZ. Cell viability analysis of ARP1 and H929 EV and TRIP13 OE cells treated with the indicated concentrations of (**A**) BTZ (**B**) Etoposide and (**C**) Melphalan for 24h by trypan blue staining. Data are represented as mean ± SD. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ by Student's *t* test. $n = 3$ per condition.



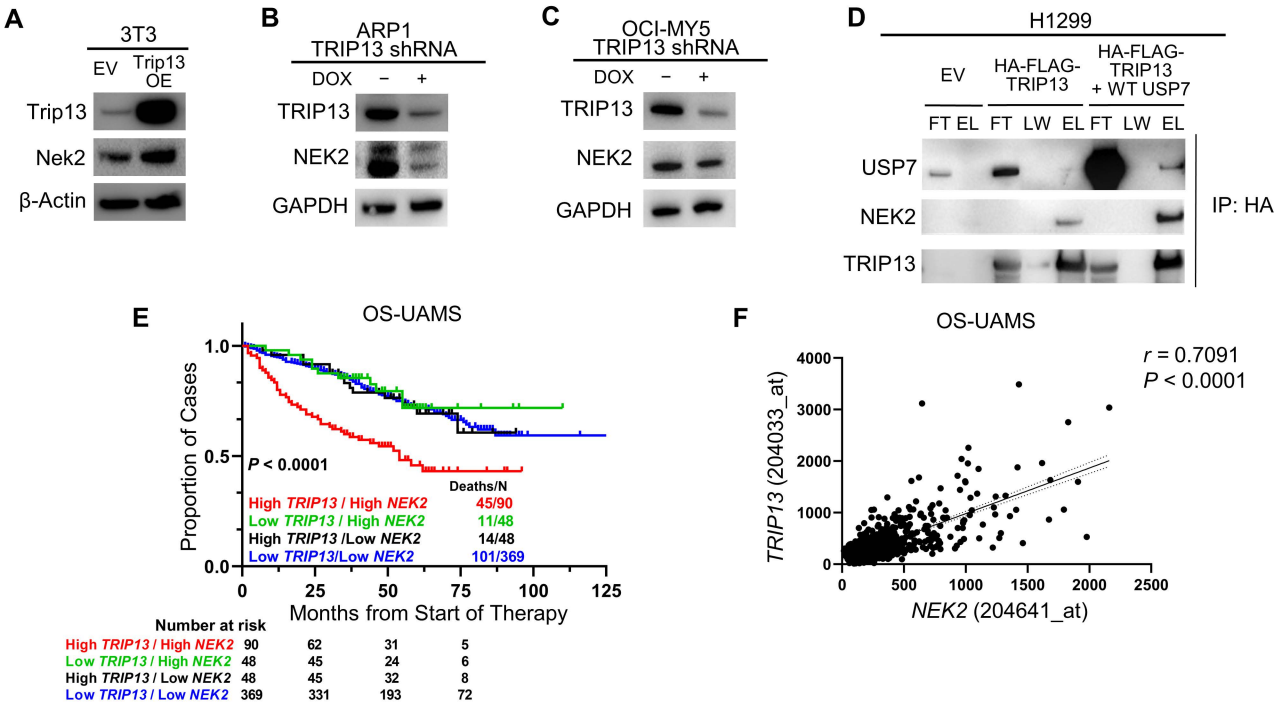
Supplemental Figure 4. TRIP13 enhances cellular protein deubiquitination. Western blot analysis of Ub, TRIP13, and β-ACTIN of H929 EV and TRIP13 OE cells treated with or without BTZ for 6 hours.



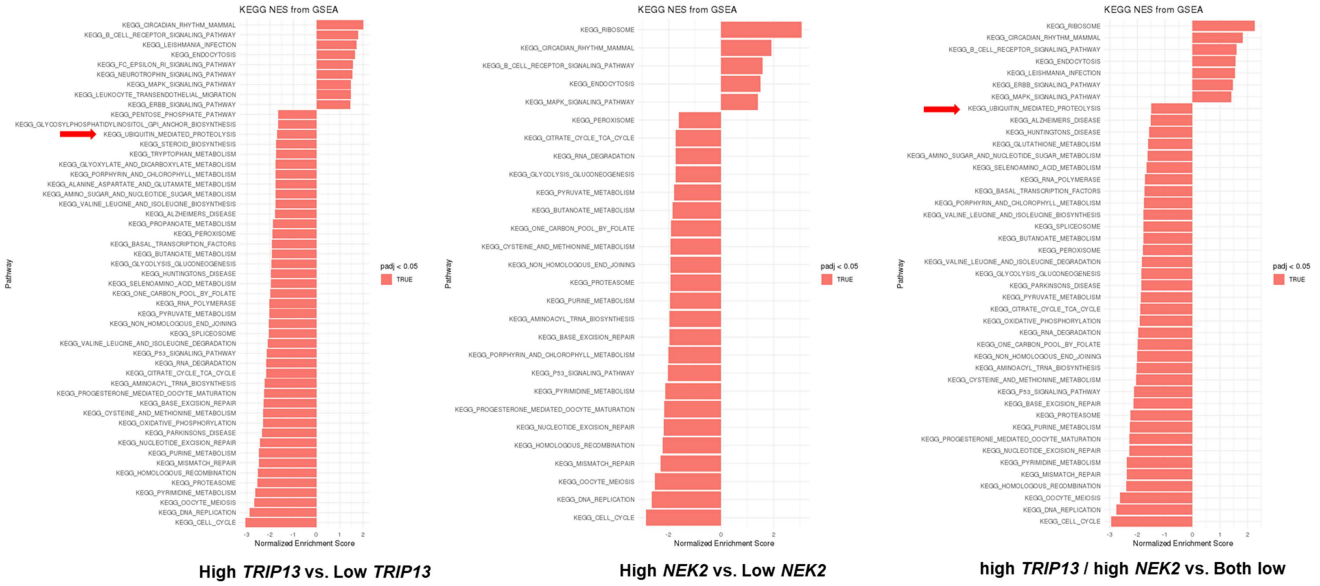
Supplemental Figure 5. High TRIP13 is sensitive to USP7 inhibitor P5091. Cell viability analysis of ARP1 EV and TRIP13 OE cells treated with the indicated concentrations of (**A**) PYR-41, (**B**) PR-619, (**C**) Spautin-1, and (**D**) P5091 for 24h using the MTT assay as described in methods. Data are represented as mean ± SD. * $P \leq 0.05$, ** $P \leq 0.01$ by Student's *t* test. $n = 3$ per condition.



Supplemental Figure 6. TRIP13 enhances cellular deubiquitination by binding USP7. TRIP13-HA immunoprecipitation followed by western blot analysis of USP7 and HA in H1299 cells transfected with HA-FLAG-TRIP13 and WT USP7.



Supplemental Figure 7. TRIP13 plays a critical role in stabilizing the USP7 target, NEK2. (**A**) Western blot analysis of Trip13, Nek2 and β-Actin in 3T3 EV and Trip13 OE cells. Western blot analysis of TRIP13, NEK2, GAPDH in (**B**) ARP1 cells or (**C**) OCI-MY5 cells, stably transfected with a DOX-inducible TRIP13 shRNA, following 48h of treatment with or without DOX. (**D**) TRIP13-HA immunoprecipitation from H1299 transfected with EV, HA-FLAG-TRIP13 alone or HA-FLAG-TRIP13 in combination with WT USP7, followed by western blot analysis of USP7, NEK2 and TRIP13 in the FT, LW and E fractions. (**E**) Kaplan-Meier analysis of MM patients from the UAMS dataset with high *TRIP13* and high *NEK2* relative to MM with low expression of one or both genes ($P < 0.0001$ by log-rank test). (**F**) Scatter plot of *NEK2* and *TRIP13* gene expression from the UAMS dataset. Pearson's correlation (r) values and corresponding P value are indicated.



High *TRIP13* vs. Low *TRIP13* | **High *NEK2* vs. Low *NEK2*** | **high *TRIP13* / high *NEK2* vs. Both low**

Supplemental Figure 8. Ubiquitin-mediated proteolysis pathways are enriched in MM with high-*TRIP13*. Bar graphs of significantly enriched KEGG pathways features in the CoMMpass dataset based on differential expression of *TRIP13* and/or *NEK2*. Negative enrichment scores correspond to high expression of the gene of interest.

Supplemental Figure 9. USP7 phosphorylation has no correlation with expression of TRIP13. Western blot analysis of TRIP13, USP7, Phospho-USP7 (P-USP7) and GAPDH in (**A**) ARP1 EV and TRIP13 OE cells and (**B**) ARP1 TRIP13 shRNA cells treated with or without DOX for 48 hours.